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STUDIES IN CLAISEN REARRANGEMENT—IV

4-PHENOXYMETHYL-Δ^3-CHROMENE AS AN INTERMEDIATE IN THE FORMATION OF 6H-BENZOFURO(3·2-c)[1]-(11a,6a-DIHYDRO-11a-METHYL)BENZOPYRAN

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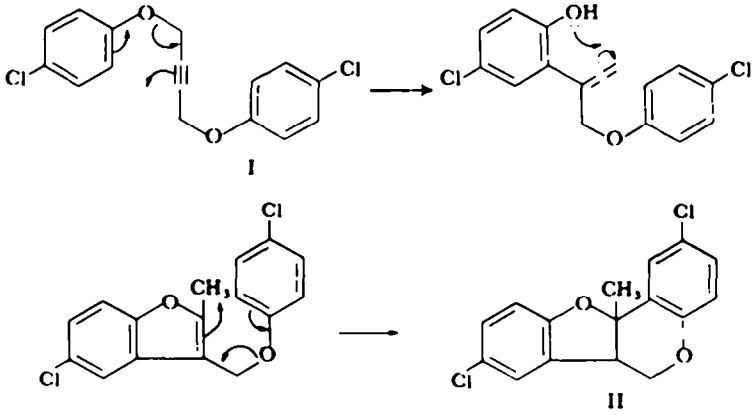
Abstract—Of two conceivable mechanistic pathways in the conversion of 1,4-diaryloxy-2-butynes to benzofurobenzopyrans, one is eliminated and the other validated. Whereas 2-methyl-3-phenoxymethylbenzofuran is resistant to Claisen rearrangement, 4-phenoxymethyl-Δ^3-chromene undergoes such a rearrangement with concomitant ring closure to the benzofurobenzopyran (VIII). The related system viz. 4-phenoxymethylcoumarin showed no propensity for similar rearrangement.

IN AN earlier investigation,[1] the thermal rearrangement of 1,4-di-(*p*-chlorophenoxy)-but-2-yne (I) to the benzofurobenzopyran (II) was reported. The presence of the coumaran skeleton in the final product led us to propose the following mechanistic pathway for the rearrangement:



The well-established equilibrium between the anion of *ortho* allenylphenol[2] and that of 2-methylbenzofuran underscored the reasonableness of such a mechanism. Additionally, instances are known where an allylic unsaturation forming part of a ring system participates in a Claisen rearrangement.[3]

The easy accessibility of 2-methyl-3-chloromethylbenzofuran[4] (III) provided an opportunity to test the validity of the suggested mechanism. A bimolecular displacement of the allylic chloride in III with phenol in the presence of potassium carbonate

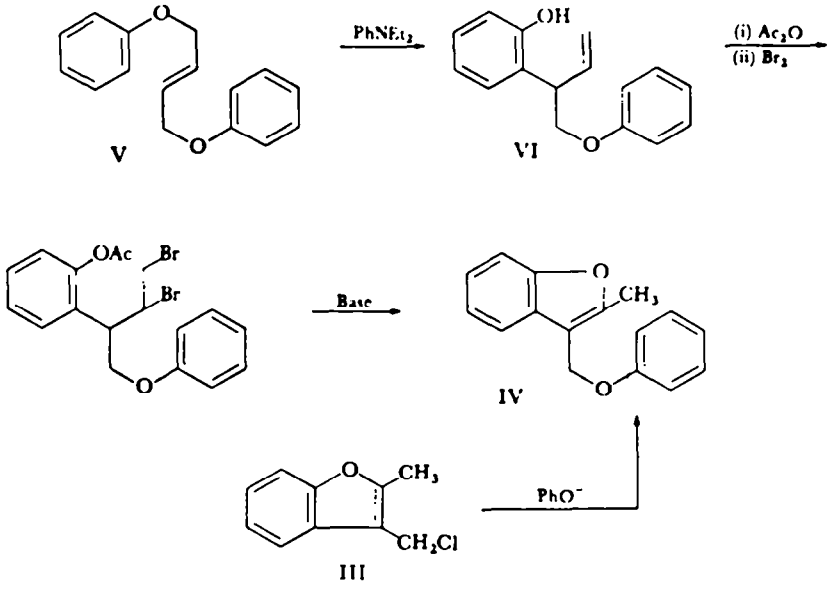
[1] B. S. Thyagarajan, K. K. Balasubramanian and R. Bhima Rao, *Tetrahedron Letters* No. 21, 1393 (1963).

[2] R. Gaertner, *J. Am. Chem. Soc.* **73**, 4400 (1951).

[3a] W. J. LeNoble, P. J. Crean and B. Gabrielson, *J. Am. Chem. Soc.* **86**, 1649 (1964); [3b] J. F. Arens, H. Olman and A. Graveland, *Rec. Trav. Chim.* **83**, 301 (1964).

[4] R. Gaertner, *J. Am. Chem. Soc.* **74**, 5319 (1952).

afforded in good yield the required intermediate, 2-methyl-3-phenoxymethyl-benzofuran (IV). The structure of this product was amply borne out by its NMR spectrum. An alternative synthesis provided additional confirmation. Claisen rearrangement of 1,4-di-phenoxy-*trans*-2-butene (V), afforded the phenol VI.* Through the sequence of reactions[6] illustrated below, it was converted into 2-methyl-3-phenoxymethylbenzofuran, identical in every respect with IV obtained earlier.



1,4-di-phenoxy-but-2-yne (VII) was rearranged in the same manner as its *p*-chloro analogue[1] and gave in 60% yield the corresponding benzofurobenzopyran (VIII). Thus with the final product VIII and the proposed intermediate IV on hand, an attempt was made to rearrange IV under the same conditions when VII yielded VIII. However in the event, the starting material was recovered unchanged. The likelihood of IV being the intermediate in the formation of VIII was thus rendered unlikely.

Iwai *et al.*[6] had reported the formation of Δ^3-chromene from the thermal rearrangement of phenyl propargyl ether. Analogously, one might expect the formation of 4-phenoxymethyl-Δ^3-chromene (IX) from the rearrangement of VII. Consequently, it was of interest to synthesize such an intermediate and study its behaviour under the conditions of rearrangement of VII.

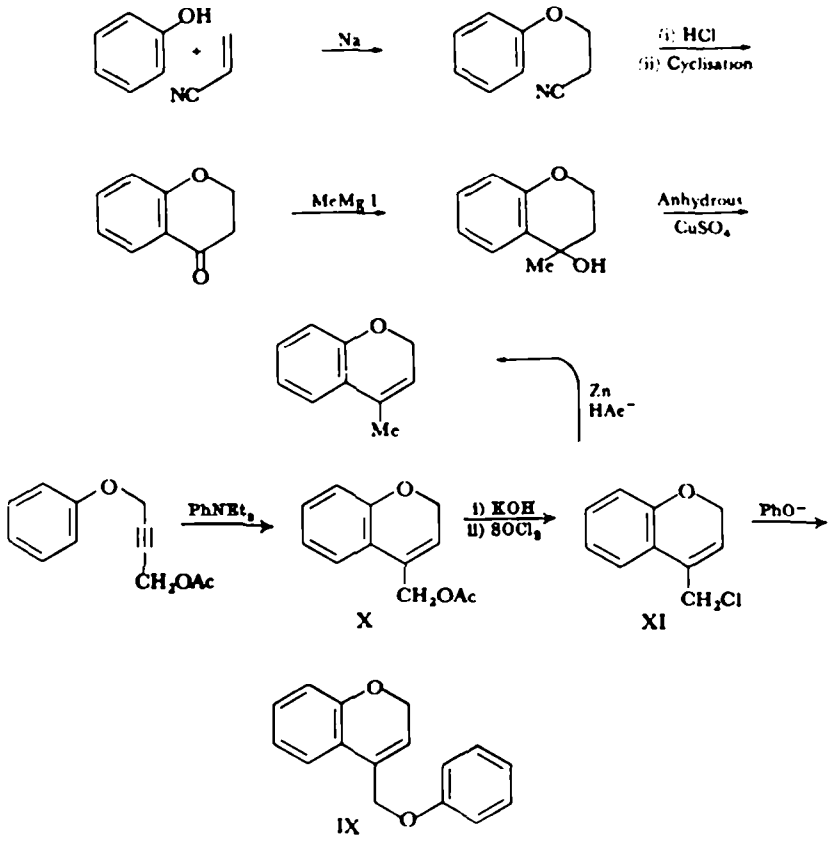
The synthesis of IX was achieved by two separate routes. One of these involved the rearrangement of 1-phenoxy-4-acetoxybut-2-yne under the Iwai conditions,[6] affording 4-acetoxymethyl-Δ^3-chromene (X). This was converted by alkaline hydrolysis and subsequent treatment with thionyl chloride into 4-chloromethyl-Δ^3-chromene (XI). Treatment of XI with phenol afforded IX. The structure of XI was also

* An extensive investigation of rearrangements of related 1,4-di-aryloxy-*trans*-2-butenes has been carried out and will form subject matter of a subsequent publication.

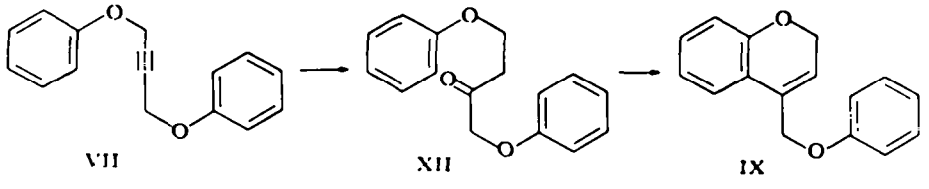
[1] R. Adams and R. E. Rindfusz, *J. Am. Chem. Soc.* **41**, 648 (1919).

[6] I. Iwai and J. Ide, *Chem. Pharm. Bulletin, Tokyo* **11**, 1042 (1963).

confirmed by its reduction to 4-methyl-Δ^3-chromene which was identical with a specimen obtained by alternative methods.[7]



A second approach to the synthesis of IX was adopted employing hydration of the triple bond in VII. Mercuric sulfate catalysed hydration of phenyl propargyl ether gave phenoxyacetone. Consequently, it was anticipated that similar hydration of VII would afford the ketone XII which may subsequently be cyclized to IX.

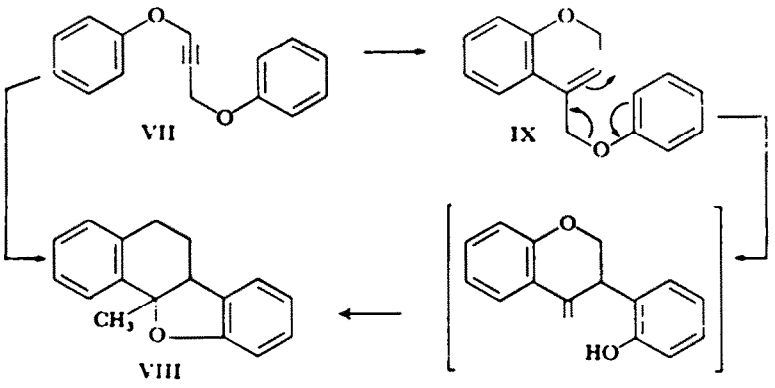


However, in the event, the product of hydration was not the ketone but the desired chromene itself. The 4-phenoxymethyl-Δ^3-chromene obtained thus was identical with that obtained by the earlier procedure (*vide supra*). This unusual mercuric-sulfate-acid-catalysed ring closure deserves special mention because treatment of the butyne

[7] J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr.* 325 (1958).

with acids in the absence of added sulfate affords no chromene. This is suggestive of the greater ease of cyclization of the ketonic intermediate than the butynyl ether.

With the availability of IX, its rearrangement was studied under the same conditions as were used for rearranging VII. Heating with diethylaniline for the same length of time readily afforded the benzofurobenzopyran VIII, thus establishing 4-phenoxymethyl-Δ^3-chromene as the rational intermediate in the rearrangement of VII.



The successful rearrangement of phenoxymethylchromene also shows that double bonds forming part of ring systems can participate in such rearrangements. It was of interest therefore to verify whether the related system viz. 4-phenoxymethyl-Δ^3-coumarin (XIII) would undergo an analogous rearrangement. Synthesis of XIII was achieved by reacting 4-bromomethylcoumarin[8] with phenol under the usual conditions. However, XIII failed to undergo any rearrangement. The present study thus reveals, of the three systems viz. aryloxymethylcoumarone, aryloxymethylcoumarin and aryloxymethylchromene, only the last mentioned derivative undergoes a Claisen rearrangement.

EXPERIMENTAL

M.p.s were determined with an ordinary thermometer and were not corrected. 1,4-di-phenoxy-but-2-yne was prepared according to the published procedure.[9] IR ($CHCl_3$): 3·1, 3·45, 4·75, 6·25, 6·7, 7·35, 8·2, 8·6, 9·25, 9·7, 9·8, 10·0, 10·8, 11·4 and 12·2 μ. UV (EtOH): 270 mμ (log ε 3·40).

Rearrangement of 1,4-*di-phenoxy-but-2-yne* (VII) *to the benzofurobenzopyran* (VIII)

Compound VII (10 g) was refluxed in N,N-diethylaniline (50 ml) for 10–12 hr, the soln was cooled and poured into 1:1 HCl. The mixture was extracted with ether, the extract washed with HCl till no more basic material was extracted, then washed with dil NaOHaq and finally with water. The neutral ether soln was dried ($MgSO_4$) and evaporated, the residue was triturated with EtOH (10 ml) and filtered. Recrystallized from EtOH, it melted at 124° (6 g; 60%). Found: C, 80·50; H, 5·95. $C_{16}H_{14}O_2$ requires: C, 80·65; H, 5·92%.) IR ($CHCl_3$): 3·05, 3·3, 5·8, 6·2, 6·25, 6·4, 6·8, 7·35, 8·35, 9·0, 9·20, 9·4, 9·7, 10·0, 11·0 and 11·6 μ. UV (EtOH): 278 mμ (log ε 3·63) and 203 (4·17). NMR (60 Mc $CDCl_3$): a s at 1·74 ppm, a qu at 3·45 ppm, two qus at 3·8 and 4·3 ppm, and a m at 6·5 ppm to 7·5 ppm.

2-Methyl-3-chloromethylbenzofuran (III) was prepared by the method of Gaertner.[4]

[8] B. B. Dey and Radha Bai, *J. Indian Chem. Soc.* **11**, 635 (1934).
[9] A. W. Johnson, *J. Chem. Soc.* 1009 (1946).

2-Methyl-3-phenoxymethylbenzofuran (IV)

Phenol (8·9 g) and anhyd K_2CO_3 (7 g) were refluxed in dry acetone (50 ml) containing a few crystals of KI, for 20 min. To the cooled acetone soln was added a soln of III (9·2 g) in dry acetone (25 ml) during a period of 15 min. After a further addition of dry K_2CO_3 (7 g) the mixture was refluxed with stirring for 10 hr and left at room temp overnight. It was decomposed with water, extracted with ether, washed with 10% NaOHaq and finally with water. The neutral ether soln was dried ($MgSO_4$) and evaporated to give a pale yellow mobile liquid, b.p. 144–146°/0·3 mm, yield, 11 g (90%). (Found: C, 80·67: H, 5·85. $C_{16}H_{14}O_2$ requires: C, 80·65; H, 5·92%.) IR ($CHCl_3$): 6·12, 6·25, 6·275, 6·83, 6·90, 7·17, 7·57, 7·82, 8·72, 8·5, 8·55 and 8·70 μ. UV (EtOH): 248 mμ (log ϵ 4·05) and 273 mμ (log ϵ 3·63). NMR (60 Mc, $CDCl_3$): s at 2·3 ppm, s at 4·95 ppm, and m at 6·85 to 7·6 ppm.

Preparation of 1,4-*di-phenoxy*-trans-2-*butene* (V)

This was prepared according to the procedure described[10a] for the corresponding halophenoxybutenes, m.p. 90°; reported[10b] m.p. 90°. IR ($CHCl_3$): 3·3, 3·45, 3·50, 6·275, 6·70, 6·90, 7·3, 7·7, 8·3, 8·6, 9·3, 9·7, 10·0, 10·25 and 11·4 μ. UV (EtOH): 220 mμ (log ϵ 4·29), 271 mμ (log ϵ 3·54) and 278 mμ (3·47). NMR (60 Mc, $CDCl_3$): s at 4·5 ppm, a signal at 6·0 ppm, and m at 6·7 to 7·4 ppm.

Rearrangement of V *to* VI

The ether V (10 g) was refluxed in diethylaniline (50 ml) for 10 hr. It was then taken up in ether, washed with 1:1 HCl and with water. Evaporation of the ether gave a dark viscous liquid which was distilled to yield the product, b.p. 150°/0·5 mm, yield 7·6 g (76%). (Found: C, 79·79; H, 7·1. $C_{16}H_{16}O_2$ requires: C, 80·0; H, 6·64%.) IR ($CHCl_3$): 2·95, 3·3, 3·5, 6·15, 6·25, 6·75, 6·90, 7·25, 7·60, 7·7, 8·3, 8·6, 8·7, 9·25, 9·7, 10·2, 10·8, 12·4, 13·2 and 14·4 μ. UV (EtOH): 220 (log ϵ 4·20), 272 (log ϵ 3·59) and 280 mμ (log ϵ 3·56). NMR (60 Mc, $CDCl_3$): signals at 4·2, 5·2, 6 to 7, and 9·5 ppm.

Acetate of VI. VI (5 g) was dissolved in Ac_2O (25 ml) to which pyridine (15 ml) was added and refluxed for 6 hr. The mixture was poured into crushed ice, extracted with ether, the ether layer washed with sat $NaHCO_3$aq and finally with water. The dried extract was evaporated and the residue distilled to give the acetate b.p. 148°/0·5 mm, yield, 4·25 g (85%). (Found: C, 76·23; H, 6·47. $C_{18}H_{18}O_3$ requires: C, 76·57; H, 6·43%.) IR ($CHCl_3$): 3·3, 3·45, 5·72, 6·15, 6·3, 6·8, 6·9, 7·4, 7·8, 8·1, 8·5, 8·6, 9·0, 9·4, 9·7, 9·8, 10·4, 11·0, 12·2, 13·3 and 14·3 μ. UV (EtOH): 204 (log ϵ 4·25), 272 (log ϵ 3·27) and 279 mμ (log ϵ 3·17). NMR (60 Mc, $CDCl_3$): a tall s at 2·15 ppm, a m at 4·15 ppm, a t at 5·1 ppm, a t at 6·0 ppm, and a m at 6·7 to 7·5 ppm.

Bromination of the above acetate. The acetate (20 g) was dissolved in dry CCl_4 (50 ml) and the soln was cooled in ice. To this was added a soln of Br (12 g) in dry CCl_4 (50 ml) and the mixture stirred for 3 hr. The soln was then washed with sat $NaHSO_3$aq, then with water and dried ($MgSO_4$). The solvent was removed under suction and the highly viscous red liquid was too unstable to be distilled even under a high vacuum, yield, 28 g. The crude dibromide was used as such for the next step of cyclization.

Cyclization of the dibromide to 2-methyl-3-phenoxymethylbenzofuran (IV)

To a soln of KOH (34 g) in EtOH (125 ml) was added a soln of the dibromide (28 g) in EtOH (25 ml) slowly with stirring. The mixture was refluxed for 4 hr and left overnight. It was then extracted with ether washed with water and dried ($MgSO_4$). Evaporation of the ether extract and distillation of the residue gave V, a pale yellow liquid, b.p. 140°/0·4 mm, yield, 7 g (50%). The IR spectrum was completely identical with that of V prepared from 2-methyl-3-chloromethylbenzofuran.

Attempted Claisen rearrangement of IV

(i) A soln of IV (2 g) in diethylaniline (10 ml) was refluxed for 10 hr under N. The cooled soln was extracted with ether, the ether extract was washed thoroughly with 1:1 HCl, then with 10% NaOHaq and finally with water. The extract was dried ($MgSO_4$) and evaporated to yield a pale red liquid (1·7 g) which was further purified by chromatography over alumina in pet. ether (40–60°). This showed an IR spectrum identical with that of the starting material.

[10a] C. L. Moyle, U.S. Patent No. 2,488,499 (1949). *Chem. Abstr.* **43**, 4419f (1949). [b] B. W. Horrow and H. E. Zaugg, *J. Am. Chem. Soc.* **79**, 1754 (1957).

(ii) The rearrangement was carried out by refluxing for 40 hr. No rearrangement product was obtained.

(iii) The compound was heated without any solvent at 250–280° under N for 7 hr. With the usual work up, no rearrangement product could be detected.

Synthesis of 4-phenoxymethyl-Δ^3-chromene (IX)

(a) *1-Phenoxy-2-butyne-4-ol.* Phenol (14 g) and KOH (9·4 g) were dissolved in EtOH (100 ml) and to this soln was added 4-chloro-2-butyn-1-ol (15 g).[11] The mixture was refluxed for 6 hr with stirring. The cooled alcoholic soln was taken in ether, washed with water, and dried ($MgSO_4$). Removal of ether gave a liquid, b.p. 130°/0·7 mm. Reported[11b] b.p. 161°/10 mm, yield, 18 g (72%).

(b) *1-Phenoxy-4-acetoxy-2-butyne.* A mixture of the alcohol (24 g), fused AcONa (4·3 g) and Ac_2O (30·6 g) were refluxed for 6 hr and left overnight. The soln was poured into ice-water, extracted with ether, the extract washed with sat $NaHCO_3$aq and finally with water. The dried ether extract on evaporation afforded the acetate which was distilled under a vacuum, b.p. 158–162°/5 mm, reported[11b] b.p. 135°/3 mm, yield (18 g). IR ($CHCl_3$): 3·2, 3·35, 5·65, 6·1, 6·6, 6·7, 7·1, 7·55, 8·0, 8·4, 8·6, 9·1, 9·5, 9·9, 10·2, 10·8, 11·15, 11·7, 12·0, 12·5, 12·7, 13·0 and 13·8 μ. NMR (60 Mc, $CDCl_3$): a s at 2·1 ppm, a s at 4·7 ppm, and a m at 6·2 to 7·4 ppm.

(c) *Rearrangement of the above acetate to 4-acetoxymethyl-Δ^3-chromene* (X). The above acetate (18 g) was refluxed in diethylaniline (90 ml) for 18 hr. The solvent was removed under a vacuum. The residue was taken up in ether, the ether extract washed with 1:1 HCl and dried ($MgSO_4$). The pale red liquid was distilled at 150–154°/5 mm, yield (9 g, 50%). The compound readily decolorized Br in CCl_4 forming an unstable bromo derivative, m.p. 98–104° with dec. (Found: C, 70·51; H, 5·98. $C_{13}H_{13}O_3$ requires: C, 70·58; H, 5·92%.) IR ($CHCl_3$): 3·3, 3·45, 5·825, 6·25, 6·35, 6·75, 6·95, 7·25, 7·70, 8·2 and 8·8 μ. NMR (60 Mc, $CDCl_3$): a s at 2 ppm, a q at 4·75 ppm, a d at 4·85 ppm, and a m at 7·0 ppm.

(d) *4-Hydroxymethyl-Δ^3-chromene.* A mixture of X (15 g), water (75 ml), KOH (15 g) and EtOH (25 ml) were refluxed for 4 hr. The mixture was cooled and extracted with ether. The ether extract was washed with water and dried ($MgSO_4$). Removal of ether furnished the desired 4-hydroxymethyl-Δ^3-chromene, b.p. 120°/0·5 mm, yield, 8·5 g (75%). The distilled liquid was used as such for the subsequent experiment. IR ($CHCl_3$): 2·8, 3·0, 3·5, 6·1, 6·25, 6·28, 6·75, 6·9, 7·3, 7·7, 7·9 and 8·2 μ.

(e) *4-Chloromethyl-Δ^3-chromene* (XI). To an ice-cold soln of the above hydroxy compound (20 g) in a mixture of dry ether (100 ml) and dry pyridine (10 ml) was slowly added distilled $SOCl_2$ (15 g). The mixture was stirred for 4 hr and decomposed with ice. The aqueous mixture was extracted with ether, the extract was washed with sat $NaHCO_3$aq and then with water. Evaporation of the ether extract after drying ($MgSO_4$) furnished a dark mobile liquid which was distilled in a vacuum, b.p. 100°/0·5 mm, yield (9 g; 38%). The colourless liquid slowly turned brown. (Found: C, 66·9; H, 5·36. $C_{10}H_9OCl$ requires: C, 66·47; H, 4·99%.)

(f) *4-Phenoxymethyl-Δ^3-chromene* (IX). To a soln of phenol (6 g) and KOH (3 g) in EtOH (15 ml) was added compound XI (6 g) and the mixture was refluxed for 6 hr. It was extracted with ether, washed with dil. alkali, then with water and dried ($MgSO_4$). Evaporation of the ether and distillation of the residue *in vacuo* gave IX, b.p. 154°/0·5 mm, yield (2·5 g, 24%). (Found: C, 80·43; H, 6·01. $C_{16}H_{14}O_3$ requires: C, 80·65; H, 5·92%.) IR ($CHCl_3$): 3·2, 3·5, 4·3, 6·1, 6·25, 6·7, 6·9, 7·3, 7·7, 8·2, 8·5, 8·9, 9·25, 9·7, 9·9, 11·3, 11·7, 12·3, 13·2 and 14·5 μ. UV(EtOH): 216, 268 and 308 mμ. NMR (60 Mc, $CDCl_3$): a singlet at 5·0 ppm, a triplet at 6·0 ppm and a multiplet at 6·8 to 7·5 ppm.

Reduction of 4-chloromethyl-Δ^3-chromene to 4-methyl-Δ^3-chromene

A mixture of XI (3 g), Zn dust (6 g) and 90% AcOH (30 ml) was heated on a water-bath for 4 hr and left overnight. It was then taken in ether, washed with sat $NaHCO_3$aq, then with water and dried. Evaporation of the ether furnished a pale mobile liquid, b.p. 92°/5 mm, yield, 2·5 g. The VPC of this liquid was identical with that of authentic 4-methyl-Δ^3-chromene, prepared by the method of Colonge *et al.*[7]

Hydration of phenylpropargyl ether

A mixture of phenyl propargyl ether (7 g) and mercuric sulfate (1 g) in AcOH (30 ml) was heated on a water-bath for 3 hr. The acidic soln was filtered, the pptd Hg was washed well with ether and

[11a] W. J. Bailey and E. Fujiwara, *J. Am. Chem. Soc.* 77, 165 (1955); [b] J. Colonge and G. Poilane, *Bull. Soc. Chim. Fr.* 813 (1959).

the combined filtrate taken up in ether. The ether extract was washed with dil NaOHaq, then with water, dried ($MgSO_4$) and distilled. The pale red viscous liquid was distilled at 100°/5 mm, yield (4 g; 50%). It readily formed a 2,4-DNP derivative, m.p. 130–132° and did not depress the m.p. of an authentic specimen.[15] The IR spectra and the VPC of the two ketones were identical.

Attempted hydration of 1,4-*di-phenoxy-but-2-yne*

1,4-Di-phenoxy-but-2-yne (9·6 g) was dissolved in AcOH (50 ml) to which mercuric sulfate (3 g) was added and the mixture was heated on a water-bath for 5 hr. It was then extracted with ether, washed with sat. $NaHCO_3$aq, then with water and dried ($MgSO_4$). Removal of ether furnished a viscous pale red liquid which was distilled at 146–148°/0·5 mm, yield (3 g, 30%). The IR spectrum of this liquid was completely identical with that of IX, obtained earlier (*vide supra*). The NMR spectra of the two specimens were also identical.

Rearrangement of IX *to* VIII

A soln of IX (1 g) in diethylaniline (5 ml) was refluxed for 8 to 10 hr in a N atm. The basic soln was cooled, extracted with ether, the ether extract washed with 1:1 HCl and then with water. The dried ($MgSO_4$) extract was evaporated and the crude solid was triturated with a little MeOH and filtered. It was crystallized from EtOH, m.p. 124°. Mixed m.p. with specimen obtained by rearrangement of 1,4-di-phenoxy-but-2-yne under identical conditions showed no depression, yield (0·6 g).

4-Methylcoumarin was prepared according to the procedure described in *Organic Syntheses*, Coll Volume, III; 581 (1955). 4-Bromomethylcoumarin was prepared by the procedure described[16] for 7-acetoxy-4-bromomethylcoumarin. 4-Bromomethylcoumarin melted at 175°, reported[7] m.p. 176°.

4-*Phenoxymethylcoumarin* (XIII)

A mixture of anhyd K_2CO_3 (3·4 g) and phenol (6 g) were stirred for 30 min in dry acetone (100 ml). To this was added 4-bromomethylcoumarin (3·4 g) and stirring continued for 20 hr. The mixture was filtered, the filtrate concentrated to about 25 ml and diluted with water (100 ml). The pptd solid was filtered off and washed with aqueous EtOH to remove any phenol adhering to the solids, yield (3·4 g, 98%). The analytical sample recrystallized from EtOH, m.p. 127°. (Found: C, 76·03; H, 4·91. $C_{16}H_{12}O_3$ requires: C, 76·19; H, 4·76%.) IR ($CHCl_3$): 5·9, 6·15, 6·25, 6·35, 6·7, 6·9, 7·5, 8·3, 8·5, 8·8, 9·2, 9·7, 9·9, 10·6, 11·4, 11·8 and 12·0 μ. UV (EtOH): 208 (log ε 4·39), 268 (log ε 4·05) and 308 mμ (log ε 3·77).

Attempted rearrangement of XIII

(i) A soln of XIII (1 g) in diethylaniline (5 ml) was refluxed for 14 hr and the brown soln was then acidified with 1:1 HCl. The pptd solid was filtered, washed with dil acid and with water. Recrystallized from EtOH, the solid showed m.p. and mixed m.p. with starting material 125–126°.

(ii) Compound XIII (0·5 g) was heated in a Woods metal bath at 280–300° for 5 hr in a N atm. No tangible product could be isolated from the reaction.

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[15] C. D. Hurd and P. Perletz, *J. Am. Chem. Soc.* **68**, 38 (1946).
[16] T. R. Seshadri and J. M. Sehgal, *J. Sci. Ind. Res.* **12B**, 346 (1953).